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10/574,157	03/28/2006	Herman Augustinus De Kock	TIP0051USPCT	7766

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EXAMINER	
FIERRO, ALICIA	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,157	DE KOCK ET AL.	
	Examiner	Art Unit	
	ALICIA L. FIERRO	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-19 are pending in the instant application, filed March 28, 2006. Further, according to the amended Listing of the Claims, filed on March 28, 2006, claim 20 was cancelled and claims 1-12 and 14-19 were amended.

Priority

2. The instant application is a national stage entry of PCT/EP2004/52382, filed September 30, 2004, which claims priority from U.S. Provisional Application No. 60/507,996, filed October 2, 2003 and European Patent Application No. 03103630.4, filed September 30, 2003. Insofar as the instant claims 12-19 are not enabled for making "prodrugs" and "metabolites" of claimed compounds (see rejections below), the examined claims 12-19 do not have support in the priority documents and are thus examined with an effective filing date of September 30, 2004.

Information Disclosure Statement

3. No Information Disclosure Statement has been filed in the instant application. Applicants are reminded of their duty to disclose all information known to them to be material to patentability as defined in 37 C.F.R. 1.56.

Specification Objections

4. The Examiner requests that the phrase "such a sarginine" in lines 3-4 on page 37 of the

specification be changed to "such as arginine" to correct the typing error.

Claim Objections

5. Claims 2, 4, and 12-19 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The objected claims are dependent upon claim 1, but fail to further limit the particular steps required in the independent claim. As it pertains to claim 2, claim 1 does not require any alkylation step as required by claim 2(a). As it pertains to claim 4, claim 1 does not require any amination step, or any step for the synthesis of compound (5). As it pertains to claims 12-19, claim 1 does not require any amination step as required by claim 12(a). The steps of claim 12 begin with the amination of a compound of formula (6) and ultimately produce a compound of formula (9), although claim 1 is drawn to a method of making a compound of formula (6).

6. Claim 12 is objected to because it is unclear what Applicant intends to claim, as the claim ends with the word “and.” Also, all claims must end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

(First Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-19 recite the limitation, "metabolites thereof" in reference to a method of making compounds of formula (9) and their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters, and **metabolites**. Applicant has not described the claimed genus of "metabolites" in a manner that would indicate they were in possession of the full scope of this genus, or even to describe what this genus is comprised of.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." Eli Lilly, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter aria*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lilly and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims are drawn to a method of making compounds of formula (9) and their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters, and **metabolites**. The claimed "metabolites thereof" encompass any compound that contains the identical core as the compounds of formula (9), which would be produced as a result of the compound's metabolism. Applicants describe no "metabolites thereof" other than mentioning in the specification that "whenever used in the present invention the term 'compounds of the invention' or 'benzoxazole sulfonamide compounds' or a similar term is meant to include the compounds of general formulas (3), (6), (7), (8), and (9) and any subgroup thereof. This term also refers to their N-oxides, salts, stereoisomeric forms, racemic mixtures, pro-drugs, esters and metabolites" (specification page 36, lines 14-18). While various compounds of formula (9) are disclosed, there is no disclosure of a method for making any so-called metabolite. No metabolites are described in such as way as to allow one skilled in the art to ascertain that Applicant is in possession of the entire scope of the claimed genus. Applicants have not

described this genus in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the myriad of compounds embraced by the claimed "metabolites thereof," and thus for the method of making those compounds.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

8. Claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *N*-oxides, salts, stereoisomeric forms, and esters, does not reasonably provide enablement for **prodrugs**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether

a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

The Nature of the Invention

The instant invention is drawn to a method of preparing a compound of Formula (9), salts, N-oxides, stereoisomers, racemic mixtures, esters, metabolites, and prodrugs thereof. Finding a prodrug is an empirical exercise. Predicting, for example, if a certain compound is in fact a prodrug that produces the active compound metabolically at a therapeutic concentration and a useful rate, is filled with experimental uncertainty. Attempts have been made to predict drug metabolism *de novo,* but this is still an experimental science. A prodrug of a compound must meet three tests. It must itself be biologically active. It must be metabolized to a second substance *in vivo* at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria requires a clinical trial setting and a large quantity of experimentation.

The State of the Prior Art

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized in vivo into an active metabolite. As

disclosed in Stella (Expert Opinions *Prodrugs as therapeutics*), "prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism, and targeting limitations" (277). Stella, Valentino J, Expert Opinion of Therapeutic Patents, *Prodrugs as therapeutics*, 2004 14(3): 277-280. Wolff et al. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pgs. 975-977, 1994) summarizes the state of the prodrug art, the lengthy research involved in successfully identifying a prodrug, and difficulties of extrapolating between species. With the limited direction and exemplification the specification offers, it is highly unpredictable whether or not the compounds of the Formula (9) will actually form effective prodrugs. Testa, Bernard, Biochemical Pharmacology, *Prodrug Research: futile or fertile?* 68 (2004) 2097-2106, discloses, on page 2098, the various challenges in prodrug research, concluding that all of these challenges may render prodrug optimization difficult to predict and achieve. Finally, Ettmayer, Peter, Medicinal Chemistry, *Lessons Learned from Marketed and Investigational Prodrugs,* 47(10) (2004) 2394-2404, discloses, on page 2401, that "the prodrug strategy should only be considered as a last resort to improve the oral bioavailability of important therapeutic agents" and "At the beginning of each prodrug program, there should be a clear definition of the problem to solve and defect to improve. The prodrug approach should not be misunderstood as a universal solution to all barriers to a drug's usefulness, and on page 2402, "The majority of all prodrug approaches face the challenge of identifying the optimal prodrug plus its activation system to enhance or prolong the concentration of the active principle at the site of action. Because of the complex situation of prodrug transport and processing, we recommend, especially for novel prodrug principles, that

the first step should be to design and investigate different prodrug prototypes of high diversity (different attachment sites, linkers, promoieties, hydrolytic, oxidative, reductive activation, chemical vs. enzymatic activation).” Ettmayer et al. concludes that "the focus on victorious prodrugs should not be misunderstood as neglecting the inherent difficulties and additional layers of complexity a prodrug strategy might face." The evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

The Level of Skill in the Art and the Predictability or lack thereof in the art

The level of skill of the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art, the more information in support of the invention is required to satisfy the statute. See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Each embodiment of a prodrug must be supported by this invention in order to be enabled for the full range of prodrugs of compounds of the Formula (9).

The Amount of Direction or Guidance Present

The specification discloses in ¶ [0299] only that “the present invention also relates to HIV protease inhibitors of formula (9) or any pharmaceutically acceptable salt or prodrug thereof.” Applicant gives no indication of what is meant by the term "prodrug" or what

compounds might reasonably be encompassed by this term. This disclosure is directed to any pharmaceutically acceptable prodrug; however, as discussed above, it would be necessary for Applicant to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others. There are no working examples in the specification that show how to make or use prodrugs of the instantly claimed compounds. Additionally, the lack of examples in the specification is not sufficient to enable one skilled in the art to which it pertains to make and use any pharmaceutically acceptable prodrug as interpreted broadly by one of ordinary skill in the art. The specification does not adequately enable a method of making all prodrugs of the compounds that the claims encompass, as defined in the instant specification. The specification has limited exemplification thereof and of the necessary starting materials, as discussed *supra*.

As stated in Morton International Inc. v. Cardinal Chem, Co., 28 USPQ2d 1190:

> [T]he specification purports to each, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However... there is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds..., there is...no evidence that such compounds even exist.

The same circumstance is true here.

The Breadth of the Claims

The claims are drawn to a method of making any compound of formula (9) which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly in the instant application as is generally understood in the art. As discussed above, this broad disclosure cannot possibly enable one skilled in the art to which it pertains to

make and use any pharmaceutically acceptable prodrug due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

The specification provides no support, as noted above, for the large number of prodrugs encompassed by the claims. The quantity of experimentation needed to make and use all of the prodrugs encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons state above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff reference.

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the pertinent art would be burdened with undue experimentation study to determine whether any pharmaceutically acceptable prodrug of compounds of the Formula (9) would successfully act as prodrugs as they are known in the art. Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which prodrugs, if any, would produce desired activity with compounds of the Formula (9) with no assurance of success.

Claim Rejections – 35 USC § 112

(second paragraph)

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 1 are drawn to compounds of formula (6) and a method of preparing said compound, respectively; however, the claims are also drawn to "racemic mixtures thereof." Thus, it is unclear whether Applicant is intending the claim the compound of formula (6) and method of making said compound, or a composition of said compound and method of making said composition. For purposes of prosecution on the merits, the Examiner will interpret the claim as being drawn to the compound rather than a composition.

Claims 1-4, 6-9, 11-16, and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation that R^3 can be Het^1 or Het^2, but gives no definition for these variables. The first time that a variable appears in a claim set, it must be defined.

Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the definitions of R9, R10a and R10b, the claims recite that these groups can be optionally substituted with

aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical;

It is unclear whether the "optionally mono- or disubstituted" refers to a separate grouping of optional substituents which can be bonded to the originally recited optional substituents, or whether the "mono or disubstituted" language is attempting to further limit the originally recited optional substituents. Additionally, it is unclear which substituents the phrase "where the substituents…" is referring to.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

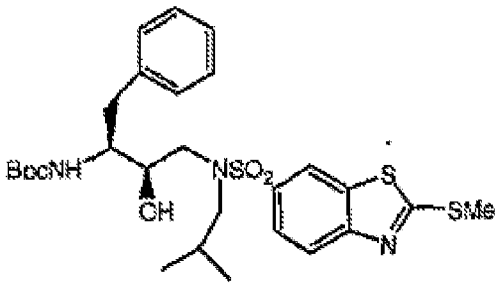
11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76.

13. Please note that for the purposes of examination on the merits, all "optionally" language of Claims 1 and 3-10 was not given patentable weight. Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. See MPEP 2111.04.

The claims are drawn to compounds of formula (6), which is a benzoxazole sulfonamide compound useful as disclosed in the production of an HIV protease inhibitor, as well as methods for their preparation. Scheme I on page 43 of the '657 publication discloses compound (i-4), which is a compound of instant formula (6), and also details its synthesis. The compound has the following structure:



(i-4)

The above compound corresponds to a compound of instant formula (6) wherein PG is Boc, R2 is H, R3 is phenylmethyl, R4 is isobutyl, E is CH_3, and the sulfamide group is attached to the benzoxazole ring at the 6 position. Compound (i-4) is the exact compound of claim 10, for which claims 6-9 are generic, with the only difference being that the benzothiazole ring in the prior art is a benzoxazole ring in the instant application, which results in the change of the S in the ring to an O. Additionally, Scheme I on page 43 teaches a method of making compound (i-4) from compound (i-1). Compound (i-1) corresponds to instant compound (2) wherein E is Me. Compound (i-1) is further sulfonated by ClSO3H to form compound (i-2), which corresponds to instant compound (3) wherein LG is Cl. Additionally, the position of the sulfanoyl group on the ring is identical to that of compound (3''') in instant claim 3. Finally, compound (i-2) is reacted with compound (i-3) to form compound (i-4). Compound (i-3) corresponds to instant compound (5), and more specifically instant compound (5') in claim 5, wherein R4 is isobutyl, R3 is phenylmethyl, R2 is H and PG is Boc. The '657 publication also details the synthesis of a compound (f-2) which is a species of the genus encompassed by formula (5), wherein PG is Boc, R3 is phenylmethyl, and R4 is methylpyridine from the compound 2S,3S-1,2-epoxy-3-(*tert*-butoxycarbonylamino)-4-phenylbutane which is a compound of instant formula (4) as in claim 4 wherein R3 is methylphenyl and PG is Boc. Although the reference is silent as to the methods of

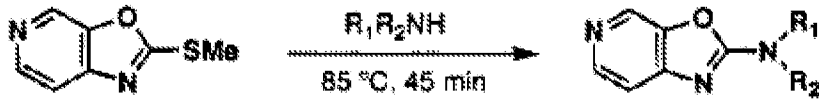
preparation of compound (i-1), in the instant case where E is CH_3 the interchange of H and CH3 is obvious. Hydrogen and methyl substitutions are known in the art and are deemed to be obvious variants of each other. *In re Wood*, 199 USPQ 137. Thus, the step of alkylating the mercapto group by adding a methyl group is an obvious variation of the known method.

14. To those skilled in the chemical art, compounds are not patentably distinct when the claimed compounds and prior art compounds have a difference of one chalcogen vs. another chalcogen. Since both O and S are chalcogens, the claimed compounds are analogues or isologues of those in the '657 publication. *Ex parte Wiseman*, 98 USPQ 277 (1953). Additionally, the instantly claimed compounds and that of the prior art are bioisosteres of one another. Patani et al. teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, O and S are isosteric (See Table 25, page 3158, compounds 52a and 52d). Case law has determined that when chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder,* 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May,* 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (steroisomers); In re *Hoch,* 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

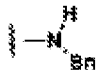
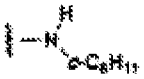
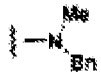
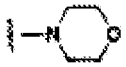
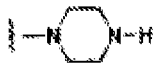
The instantly claimed compounds would have been *prima facie* obvious to one skilled in the art at the time the invention was made because one skilled in the art would have been motivated to prepare analogues or bioisosteres of the compounds taught by the '657 publication with the expectation of obtaining compounds with similar properties and utilities (namely intermediates used to produce pharmacologically active HIV protease inhibitors). Because the compounds would be *prima facie* obvious, as determined above, the methods of making as in claims 1 and 3-5 would also be *prima facie* obvious, as the steps and the structures of the intermediates used to make compound (6) are all exactly the same as the prior art, with the only difference being the substitution of the sulfur in the prior art for an oxygen in the instant claims in the starting material.

15. Claims 12-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76 as applied to claims 1-10 above, and further in view of Chu-Moyer et al., *J. Org. Chem*, 1995, 60 (17), 5721-5725.

Taken together, the above references do not teach the amination of a compound of formula (6) as required by claim 12(a). Rather, in the '657 publication compound (i-4) which corresponds to instant formula (6) is oxidized prior to the amination, and compounds (i-6 and (i-5) are aminated. However, the amination of and S-alkyl group such as S-Me is a well known nucleophilic aromatic substitution reaction. Chu-Moyer et al. teach the following compounds and reactions:



3c 9a-f

entry	compd	$-NR_1R_2$	yield (%)
1	9a		96
2	9b		92
3[a]	9c		91
4	9d		90
5	9e		94
6	9f		88

One of ordinary skill in the art would have been motivated at the time the invention was made to alter the steps of the synthesis method by directly aminating the S-Me group rather than oxidizing it first, as is taught in Scheme I. The motivation to do so is based on the fact that the reaction shown about by Chu-Moyer et al. is a well-known synthesis method which would allow for the elimination of an extra step in the method (namely the oxidation step). The '657 publication teaches that the amination step was carried out over a period of 20 hours and gave a 93% yield (page 44, lines 11 and 14), while the reaction taught by Chu-Moyer et al. was carried out for only 45 minutes, with no significant difference in yield of aminated product, as shown by the table above. The amination step in the '657 publication yields a product which corresponds to instant formula (7) wherein R8 is hydrogen and R6 is ethylpyrrolidine (Het^1C_{1-6}alkyl).

Following the amination step, the '657 patent teaches the deprotection of compound (i-7) on page 44, lines 17-23, which forms a compound that corresponds with instant compound 8.

Finally, compound (i-7) was reacted with 1-[[[[(3S,3aR,6aS)+(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]oxy]-2,5-pyrrolidinedione, which had the effect of coupling a radical of instant formula R_1-L [with the formula Het^1-O-C(=O)] to compound (i-7) to form compound 20. Compound 20 of the '657 publication corresponds to a compound of instant formula (9).

16. There would have been *prima facie* obvious motivation for one of ordinary skill in the art at the time the invention was made to combine the compounds and method taught by the '657 with the information on bioisosteres from Patani et al. to obtain compounds with similar activity, and to further combine this with the teachings on amination in Chu-Moyer et al. Chu-Moyer et al. shows that directly aminating an S-Me group is a known reaction which would allow for the synthesis of an aminated ring structure in less time than the method taught by the '657 publication while still obtaining a high yield of aminated product. This would have given *prima facie* obvious motivation to combine these three references with a reasonable expectation of success.

17. Claims 11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002/083657 A2 (Surleraux, et al.; publication date October 24, 2002) in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76, and Chu-Moyer et al., *J. Org. Chem*, 1995, 60 (17), 5721-5725 as applied to claims 1-10, 12-15 and 17-18 above, and further in view of Berge et al. *J. Pharm. Sci.*, 1977, 66 (1), 1-19.

18. Taken together, the above references do not teach the specific salt forms of compounds (6) and (9) claimed by Applicant. Berge et al. teaches the benefits of preparing salts of

pharmaceutical compounds. The reference teaches that "salt formation is a means of altering the physical, chemical, and biological characteristics of a drug without modifying its chemical structure" and further that "the salt form can have a dramatic influence on the overall properties of the parent compound" (p. 16, Conclusions section). Although the reference discloses that, at the time it was written, there was not a way to knowingly predict how a particular salt would affect the properties of a given compound, it provides many factors and considerations which would have led one of ordinary skill in the art to choose a salt form that would meet the limitations of claims 11 and 19. For example, Berge et al. teaches that "knowledge that one salt form imparts greater water solubility, is less toxic, or slows dissolution rate" would be beneficial to formulators and that sometimes generalizations can be made in this regard (page 2, column 2, paragraph 2). These factors, in turn, affect the bioavailability and formulation characteristics of a drug (p. 5, column 1, last paragraph). Additionally, salt formation is one of the first approaches considered to increase a compound's solubility in water (p.7, column 1-2). For example, the reference teaches that salt combinations with dicarboxylic acids confer water solubility on a compound if one carboxylic group is left free (page 2, column 2, paragraph 2). In the instant case, fumarate is a dicarboxylic acid salt.

19. One of ordinary skill in the art would have been motivated at the time the invention was made to make pharmaceutical salts of the instant compounds, and specifically to utilize the claimed salts such as fumarate. Berge et al. teaches that it is desirable for pharmaceutical chemists to impart water solubility on a pharmaceutical compound by creating, for example, dicarboxylic acid salts such as fumarate which are known to confer water solubility on a

compound. This would lead to *prima facie* obvious motivation to combine these references with a reasonable expectation of success.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALICIA L. FIERRO whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/A. L. F./
Examiner, Art Unit 4121

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121